

Amendments to the Drawings:

The attached sheets (see, Appendix) of drawings include changes to Figures 3 and 4 and replace original drawing sheets 3, 5, 6, 7, and 8.

In Sheet 3 (Figure 3, sheet 1 of 3), a previously omitted base has been added to the 3' end of the primer sequence of CM-F to match SEQ ID NO: 1 in the sequence listing.

In Sheet 5 (Figure 3, sheet 3 of 3), the primer sequence for CM-R has been replaced with the sequence set forth in SEQ ID NO: 2 but in the 3'-to-5' orientation. SEQ ID NO: 2 is set forth in the sequence listing in the standard 5'-to-3' orientation.

In Sheet 6 (Figure 4, sheet 1 of 3), a previously omitted base has been added to the 3' end of primer sequence of 1AD-F to match SEQ ID NO: 5 in the sequence listing.

In Sheet 6 (Figure 4, sheet 1 of 3), a previously omitted base has been added to the 3' end of primer sequence of 1B-F to match SEQ ID NO: 6 in the sequence listing.

In Sheet 7 (Figure 4, sheet 2 of 3), the primer sequence for 1B-R has been replaced with the sequence set forth in SEQ ID NO: 8 but in the 3'-to-5' orientation. SEQ ID NO: 8 is set forth in the sequence listing in the standard 5'-to-3' orientation.

In Sheet 7 (Figure 4, sheet 2 of 3), "Contig 1 (1951)" and the nucleotide sequence that immediately follows it on the same line have been deleted.

In Sheet 8 (Figure 4, sheet 3 of 3), the primer sequence for 1D-R has been replaced with the sequence set forth in SEQ ID NO: 7 but in the 3'-to-5' orientation. SEQ ID NO: 7 is set forth in the sequence listing in the standard 5'-to-3' orientation.

In Sheet 8 (Figure 4, sheet 3 of 3), the primer sequence for 1A-R has been replaced with the sequence set forth in SEQ ID NO: 9 but in the 3'-to-5' orientation. SEQ ID NO: 9 is set forth in the sequence listing in the standard 5'-to-3' orientation.

In Sheet 8 (Figure 4, sheet 3 of 3), "Contig 1 (2201)" and the nucleotide sequence that immediately follows it on the same line have been deleted.

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The amendments to the drawings are fully supported by the application as filed and do not introduce new matter.

Appendix: Replacement Sheets

REMARKS/ARGUMENTS

The Application Complies with the Sequence Rules

The Office Action indicates that the application fails to comply with the sequence requirements of 37 C.F.R. §§ 1.821-1.825 because the sequences shown in Figures 3 and 4 are not identified by a SEQ ID NO nor are these sequences part of the sequence listing.

To comply with the sequence rules, Applicants submit concurrently herewith new paper and computer-readable forms of the sequence listing to replace the last filed sequence listing and have requested above that the new sequence listing be entered into the specification. The new sequence listing now includes SEQ ID NOs: 22-24 which are the sequences for the portions of AHASL1B, AHASL1D, and AHASL1A, respectively, shown in Figure 3 and also includes SEQ ID NOs: 25-27 which are the sequences for the portions of AHASL1B, AHASL1D, and AHASL1A, respectively, shown in Figure 4. Therefore, the sequences that have been added to the new sequence listing do not constitute new matter because these sequences are found in original Figures 3 and 4.

In addition, Applicants have also amended the sequence listing as follows. Applicants have renumbered SEQ ID NOs: 17 and 18 of the last filed sequence listing as SEQ ID NOs: 18 and 20, respectively, in the new sequence listing. Additionally, Applicants have added the amino acid sequences encoded by SEQ ID NOs: 16-18 of the last filed sequence listing as SEQ ID NOs: 17, 19, and 21, respectively, in the new sequence listing. These amino acid sequences that have been added to the new sequence listing do not constitute new matter because these amino sequences are set forth in original Figures 1B and 1C.

In view of the new paper and computer-readable forms of the sequence listing filed concurrently herewith and the above remarks, Applicants submit that the application fully complies with the sequence rules.

The Objection to the Specification Should Be Withdrawn

The specification has been objected to for informalities. The Office Action indicates that the description of Figure 1C does not accurately reflect the sequences contained in the figure. As discussed in the last section, Applicants have filed concurrently herewith new paper and computer-readable forms of the sequence listing in which SEQ ID NOs: 17 and 18 of the last filed sequence listing have been renumbered as SEQ ID NOs: 18 and 20, respectively, in the new sequence listing. Additionally, Applicants have added to the new sequence listing the amino acid sequences for the mutant form of AHASL1B, the wild-type form of AHASL1A, and the mutant form AHASL1A as SEQ ID NOs: 17, 19, and 21, respectively. These amino acid sequences were inadvertently omitted from the last filed sequence listing. The new sequence listing now includes all nucleotide and amino acid sequences shown in Figures 1A-1C. Furthermore, in view of the new sequence listing, the description of Figure 1C accurately reflects the sequences contained in the figure.

In view of the new paper and computer-readable forms of the sequence listing filed concurrently herewith and the above remarks, Applicants submit that the objection to the specification for informalities should be withdrawn.

The Objections to the Drawings Should Be Withdrawn

The drawings have been objected to because several of the primers (CM-F, CM-R, 1AD-F, 1B-F, 1D-R, 1B-R, and 1A-R) in Figures 3 and 4 do not match the sequences of the same name in the sequence listing.

As discussed above in the "Amendments to the Drawings" section, Applicants submit herewith replacement drawing sheets to replace drawing sheets 3 and 5-8. In the replacement sheets, the primer sequence for CM-F, CM-R, 1AD-F, 1B-F, 1D-R, 1B-R, and 1A-R match the corresponding primer sequences in the sequence listing. In addition, Applicants have removed from replacement sheets 7 and 8, the sequence referred to as "Contig 1" as this sequence was inadvertently included in original Figure 4.

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In view of the replacement sheets and the above remarks, Applicants submit that the objections to the drawings should be withdrawn.

Status of the Claims

Claims 10-13, 25-28, and 32-41 have been cancelled for being drawn to non-elected subject matter. Applicants expressly reserve the right to file one or more divisional applications or take such other appropriate measures deemed necessary to protect the subject matter of the cancelled claims.

Applicants have amended claims 1, 15, and 30 to point out more distinctly Applicants' claimed invention. In particular, Applicants have amended each of these claims to point out more distinctly that the 3'-end nucleotide of the mutant-allele-specific primer is cytidine. Applicants have further amended claims 15 and 30 to point out more distinctly that the 3'-end nucleotide of the wild-type-allele-specific primer is guanosine. Support for the amendments to the claims can be found in the specification, particularly in the first full paragraph on page 18 and in the paragraph that bridges pages 19 and 20.

No new matter has been added by way of amendment of the claims.

Claims 1-9, 14-24, and 29-31 are pending.

Reexamination and reconsideration of the application as amended are respectfully requested in view of the following remarks.

Claim Objections

The Detailed Action section (p. 14) of the Office Actions indicates that claims 6, 9, 20, and 24 have been objected to for being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims. The Office Action Summary, however, indicates that claims 4, 6, 9, 18,

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20, and 24 are objected to. The Detailed Action does not further describe the objections to claims 4 and 18.

Because Applicants are unaware of the bases for the objections to claims 4 and 18, Applicants are unable in the instant response to address these objections. Applicants respectfully invite the Examiner to either withdraw the objections or set forth with particularity in the next Office Action the reason(s) for the objections to claims 4 and 18 so as to provide Applicants an opportunity to properly address these objections.

The Rejection of the Claims under 103(a) Should Be Withdrawn

Claims 1-5, 7-8, 14-19, 21-23, and 29-31 have been rejected under 35 U.S.C. § 103(a). Claims 1, 15, and 30 have been amended. This rejection is respectfully traversed.

Claims 1, 7, 8, 14, 15, 21-23 and 29 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Hucl *et al.* (WO 2003/014357) in view of DelRio-LaFreniere *et al.* (2001). The Office Action indicates that Hucl *et al.* teaches the use of genomic DNA of step (a) of claim 1 and the portion of AHASL1 nucleotide sequence responsible for the imidazolinone mutation, including nucleotides of 3-23 of SEQ ID NO: 12 of the instant application. Regarding claim 7, the Office Action further indicates that Hucl *et al.* teaches the AHASL1 sequence that includes the sequence that is relevant to SEQ ID NO: 3 of the instant application. Regarding claim 8, the Office Action indicates that Hucl *et al.* teaches that there are AHAS genes on genomes A, B, and D of the *Triticum* wheat plant and additionally teaches the sequence of the Imi1 gene wheat gene, which is the AHASL1D gene on the D genome as evidenced by Pozniak *et al.* (2004).

Regarding claims 15, 21, and 23, the Office Action indicates that the teachings of Hucl *et al.* are applied to steps (a), (b), and (d) of claims 15, 21, and 23 as they were applied to claims 1, 7, and 8 and that Hucl *et al.* additionally teaches the wild-type AHASL1 nucleic acid sequence that includes the sequence relevant to SEQ ID NO: 10 of the instant application. Regarding claim 21, the Office Action indicates that Hucl *et al.* teaches the AHASL1 sequence that includes the sequence that is relevant to SEQ ID NO: 3 of the instant application. Regarding claim 22, the

Office Action indicates that Hucl *et al.* teaches the AHASL1 sequence that includes the sequence that is relevant to SEQ ID NO: 4. Regarding claim 23, the Office Action indicates that Hucl *et al.* teaches that there are AHAS genes on genomes A, B, and D of the *Triticum* wheat plant, and the sequence of the Imi1 gene wheat gene, which is the AHASL1D gene on the D genome as evidenced by Pozniak *et al.* (2004).

The Office Action acknowledges that Hucl *et al.* fails to teach the analysis of AHASL1 genes via allele-specific PCR using oligonucleotide primers, or primers with mismatches as are required for primers directed to nucleotides 3 to 23 of SEQ ID NO: 12 with a cytidine at the 3' end.

The Office Action indicates that DelRio-LaFreniere *et al.* teaches a method for the detection of single nucleotide polymorphisms using allele-specific primers with intentional mismatches and a PCR reaction of genomic DNA from whole blood, dNTPs, a polymerase, forward and reverse gene-specific primers, and a mutant-allele-specific primer. The Office Action indicates that DelRio-LaFreniere *et al.* teaches that the allele-specific primers contain additional mismatches and that the ideal nature and locations (e.g. antepenultimate and penultimate) of the mismatches can be experimentally determined. The Office Action indicates that DelRio-LaFreniere *et al.* teaches the use of wild-type-specific and mutant-allele specific primers that are designed to flank the polymorphic position and that additional mismatches within the primers can increase amplification specificity. The Office Action indicates that DelRio-LaFreniere *et al.* teaches the detection of PCR products using gel electrophoresis and ethidium bromide staining and the use of wild-type-allele-specific primers for the detection of wild-type-alleles.

The Office Action asserts that it would have been prima facie obvious to one of skill in the art at the time of the invention was made to have modified the mutation detection methods of Hucl *et al.* so as to have used the allele-specific amplification and primers designed with intentional mismatches of DelRio-LaFreniere *et al.* and that one would have been motivated to do so because of the teaching of DelRio-LaFreniere *et al.* that intentionally mismatched allele-specific amplification methods provide accurate results and that various intentional mismatches

can be tested for optimum specificity. The Office Action indicates that the combined methods would have necessarily included experimentation as suggested by DelRio-LaFreniere *et al.* and thus would include creating oligonucleotides with the sequences set forth in SEQ ID NO: 3 and 4.

In contrast to this position of the Office Action, Applicants' claimed invention is not obvious in view of the combination of Hucl *et al.* and DelRio-LaFreniere *et al.* Applicants' claimed invention is directed to oligonucleotide primers and methods for detecting a mutant allele of a specific, wheat *AHASL* gene and for analysis of a wheat *AHASL* gene. The methods of Applicants' claimed invention involve the use of a mutant-allele-specific primer that has a cytidine as the 3'-end nucleotide and that is capable of annealing to the complement of nucleotides 3 to 23 of SEQ ID NO: 12. As disclosed in the instant specification on pages 7, 17, 18, such a mutant-allele-specific primer, when annealed to mutant *AHASL* allele template, results in a mismatch at the 3'-end nucleotide of the primer and the site of the G-to-A point mutation in the mutant *AHASL* allele template, yet allows for the unexpected PCR amplification of the mutant *AHASL* allele but not the wild-type *AHASL* allele. As explained in the specification on pages 17-18, Applicants' invention was both surprising and unexpected in view of the teachings of Newton *et al.* (1989) *Nucl. Acids Res.* 17:2503-2516 and Wu *et al.* (1989) *Proc. Natl. Acad. Sci. USA* 86: 2757-2760 that oligonucleotides with a 3'-end-residue that is mismatched to the template DNA will not function as a primer for PCR amplification under appropriate conditions.

The Office Action indicates that claim 1 does not require that the mutant-allele specific primer has cytidine at the 3' terminus, only that the primer has a cytidine at the 3' end. While Applicants respectfully disagree with this view of the Office Action, Applicants have amended claims 1, 15, and 30 to point out more distinctly that in their claimed methods the 3'-end nucleotide or 3' terminus of the mutant-allele-specific primer is cytidine.

The Office Action fails to indicate that Hucl *et al.* and/or DelRio-LaFreniere *et al.* teaches a method for allele-specific amplification that involves a PCR primer with a mismatch at the 3'-end residue of a PCR primer. In fact, DelRio-LaFreniere *et al.* teaches that "[t]he greatest

improvement in reaction efficiency was observed when the penultimate base (one base adjacent to the mutant nucleotide) is purposefully mismatched” (p. 202, right column, last paragraph) and further teaches that “[w]e have documented that mismatches at the penultimate and antepenultimate bases on the 3’ end of the primer significantly reduce preferential amplification.” Thus, the combination of Hucl *et al.* and DelRio-LaFreniere *et al.* DelRio-LaFreniere *et al.* simply does not provide the motivation to one of ordinary skill in the art to make Applicants’ claimed invention which is drawn to methods involving the PCR amplification of a mutant wheat AHASL gene comprising the use of a mutant-allele-specific primer that has a cytidine as the 3’-end nucleotide and is capable of annealing to the complement of nucleotides 3 to 23 of SEQ ID NO: 12.

Finally, with respect to the issue of experimentation, the Office Action fails to point out that DelRio-LaFreniere *et al.* teach that determining which mismatched primers will work requires something more than merely routine testing. In particular, DelRio-LaFreniere *et al.* teach that “our experience suggests that theoretical design of these mismatched primers cannot be assumed to work, but must be *rigorously tested*. (p. 203, left column, first paragraph) (emphasis added). Applicants submit that one of ordinary skill in that art at the time of the invention would have found such *rigorous testing* of primers with various mismatches to possibly identify one that might work for allele-specific PCR amplification of a mutant wheat AHASL allele to be something akin to undue experimentation and would certainly not consider such that the mutant-allele-specific primers of the present invention to be obvious. Furthermore, DelRio-LaFreniere *et al.* when considered alone or in combination with Newton *et al.*, and Wu *et al.* teaches away from primers with a mismatches at the 3’-end nucleotide, in favor of mismatches at the penultimate and antepenultimate bases at the 3’ end of the primer.

In view of the teachings of DelRio-LaFreniere *et al.* and in further view of the teachings discussed above of Newton *et al.* and Wu *et al.* that oligonucleotides with a 3’-end residue that is mismatched to the template DNA will not function as primers for PCR amplification under appropriate conditions, one of ordinary skill in the art at the time of the invention would neither have found that that mutant-allele-specific primers of Applicants’ claimed invention to be

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obvious nor have been motivated to even experiment with primers having a mismatch at the 3'-end nucleotide for use in allele-specific PCR amplifications of wheat AHASL genes.

Accordingly, claims 1, 7, 8, 14, 15, 21-23 and 29 are not obvious in view of Hucl *et al.* and DelRio-LaFreniere *et al.*

Claims 2, 4, 5, 16, 18, 19, and 30 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Hucl *et al.* in view of DelRio-LaFreniere *et al.* (2001) and in further view of Stanton (2002) US Patent No. 6,475,736.

The Office Action indicates that teachings of Hucl *et al.* and DelRio-LaFreniere *et al.* are applied to claims 2, 4, 5, 16, 18, 19, and 30 as they were applied to claims 1, 7, 8, 14, 15, 21-23 and 29 above. The Office Action indicates that relevant to claims 2, 16, and 30 Stanton teaches that the PCR amplification step of a genotyping procedure can be modified to increase sensitivity by using nested PCR. The Office Action then asserts that the methods of claims 2, 4, 5, 16, 18, 19, and 30 would have been *prima facie* obvious in view of Hucl *et al.*, DelRio-LaFreniere *et al.*, and Stanton.

Applicants respectfully disagree with this position of the Office Action. As discussed above, Applicants have amended claims 1, 15, and 30 to point out more distinctly that in their claimed methods the 3'-end nucleotide of the mutant-allele-specific primer is cytidine. For the reasons set forth above and not repeated here for the sake of brevity, the combination of Hucl *et al.* and DelRio-LaFreniere *et al.* fails to render the claims obvious because this combination of references fails to teach or even suggest one aspect of Applicants' claimed invention: allele-specific PCR amplification comprising a mutant-allele-specific primer that has a mismatched base, particularly a cytidine, at its 3' terminus. The Office Action fails to indicate that Stanton teaches or even suggests this aspect of Applicants' claimed invention, when considered alone or in combination with the other cited references. Accordingly, claims 2, 4, 5, 16, 18, and 30 are not obvious in view of Hucl *et al.*, DelRio-LaFreniere *et al.*, and Stanton.

Claims 3, 17, and 31 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Hucl *et al.* in view of DelRio-LaFreniere *et al.* (2001) and in further view of Stanton (2002)

and in further view of Werle *et al.* (1994).

The Office Action indicates that teachings of Hucl *et al.*, DelRio-LaFreniere *et al.* and Stanton are applied to claims 3, 17, and 31 as they were applied to claims 2, 16, and 30 above. Regarding claims 3, 17, and 31, the Office Action indicates that Werle *et al.* teaches a pre-amplification of a PCR product from genomic DNA followed by treatment with exonuclease, then analysis of the exonuclease-treated PCR product using the same conditions as for PCR or genomic DNA. The Office Action then asserts that the methods of claims 3, 17, and 31 would have been prima facie obvious in view of Hucl *et al.*, DelRio-LaFreniere *et al.*, Stanton, and Werle *et al.*

Applicants respectfully disagree with this position of the Office Action. As discussed above, Applicants have amended claims 1, 15, and 30 to point out more distinctly that in their claimed methods the 3'-end nucleotide of the mutant-allele-specific primer is cytidine. For the reasons set forth above and not repeated here for the sake of brevity, the combination of Hucl *et al.*, DelRio-LaFreniere *et al.*, and Stanton fails to render the claims obvious because this combination of references fails to teach or even suggest one aspect of Applicants' claimed invention: allele-specific PCR amplification comprising a mutant-allele-specific primer that has a mismatched base, particularly a cytidine, at its 3' terminus. The Office Action fails to indicate that Werle *et al.* teaches or even suggests this aspect of Applicants' claimed invention, when considered alone or in combination with the other cited references. Accordingly, claims 3, 17, and 31 are not obvious in view of Hucl *et al.*, DelRio-LaFreniere *et al.*, Stanton, and Werle *et al.*

In view of the amendments and the above remarks, it is submitted that the rejection of the claims under 35 U.S.C. § 103(a), should be withdrawn.

CONCLUSION

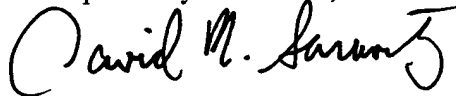
In view of the above amendments and remarks, Applicants submit that the rejections of the claims under 35 U.S.C. § 103 are overcome. Applicants respectfully submit that this application is now in condition for allowance. Early notice to this effect is solicited.

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If in the opinion of the Examiner a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned.

It is not believed that extensions of time or fees for net addition of claims are required, beyond those that may otherwise be provided for in documents accompanying this paper. However, in the event that additional extensions of time are necessary to allow consideration of this paper, such extensions are hereby petitioned under 37 C.F.R. § 1.136(a), and any fee required therefore (including fees for net addition of claims) is hereby authorized to be charged to Deposit Account No. 16-0605.

Respectfully submitted,

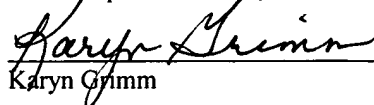


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